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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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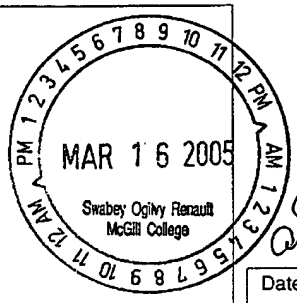

PCT

~~Reply to~~
~~WRITTEN OPINION OF THE~~
INTERNATIONAL PRELIMINARY
EXAMINING AUTHORITY
(PCT Rule 66)

Apr. 15/05 (w)

Date of mailing *(day/month/year)*	~~DUE ON MAY 09 2005~~ 09.03.2005
Applicant's or agent's file reference 15656-5PCT CC	**REPLY DUE** **within 2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2004/000011	05.01.2004	06.01.2003

International Patent Classification (IPC) or both national classification and IPC
A61K47/48, A61P25/00

Applicant
TRANSFERT PLUS et al

1. ☒ The written opinion established by the International Searching Authority:
   ☒ is ☐ is not
   considered to be a written opinion of the International Preliminary Examining Authority
2. This first report contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☒ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application
3. The applicant is hereby **invited to reply** to this opinion.

   When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(e).
   How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.
   Also: For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*. For an informal communication with the examiner, see Rule 66.6. For an additional opportunity to submit amendments, see Rule 66.4.
   If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary report on patentability (Chapter II of the PCT) must be established according to Rule 69.2 is: 06.05.2005

Name and mailing address of the International preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Gonzalez Ramon, N Telephone No. +31 70 340-3466

WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

International application No.
PCT/CA2004/000011

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this opinion is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages	
1-37	as originally filed
Claims, Numbers	
1-96	received on 22.07.2004 with letter of 22.07.2004
Drawings, Sheets	
1/20-20/20	as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-4,6-20,22-36,38-50,52-63,65-71,74-96 partially; 5,21,37,51,64,73 complete

because:

☒ the said international application, or the said claims Nos. 85-96 in relation to industrial applicability, see separate sheet relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-4,6-20,22-36,38-50,52-63,65-72,74-96 partially; see separate sheet are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search opinion has been established for the said claims Nos. 1-4,6-20,22-36,38-50,52-63,65-71,74-96 partially; 5,21,37,51,64,73 complete

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See supplemental sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. . 4, 20, 36, 50, 63 complete; 1-3, 6-19, 22-35, 38-49, 52-62, 65-72, 74-9 part

Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-3,6-19,22-35,38,39,43-46,59, 71, 72, 74-85, 88
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96
Industrial applicability (IA)	Yes:	Claims	see separate sheet
	No:	Claims	

2. Citations and explanations:

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 85-96 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

In the present application, the International Searching Authority has restricted the search under the following objections under Articles 5 and 6 PCT.

Claims 1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96 as far as related to the first invention encompass a genus of compounds defined only by their function, namely: "transporting does not affect blood brain barrier integrity" (claims 2, 18, 34, 48, 61, 72); "transporting effected by receptor mediated transcytosis or adsorptive mediated transcytosis" (claims 7, 23, 39, 53, 66, 75); "agent is releasable form said carrier after transport across the blood brain barrier" (claims 12, 28, 44, 57, 68, 80); "agent is released form said carrier after transport across the blood brain barrier" (claims 13, 29, 45, 58, 69, 81), wherein the relationship between the structural features of the members of the genus and said function have not been defined.

In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed.

It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

Therefore, claims 1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96 do not fulfil the requirements of Art. 5 and Art. 6 PCT.

Moreover present claims 1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96 relate to compounds defined by reference to vague characteristics, namely: "a functional derivative" (claims 1, 17, 33, 47, 60, 71); "a drug", "a medicine", "an anticancer agent", "a molecule active at the level of the central nervous system" (claims 3, 19, 35, 49, 62, 71); "agent has a maximum molecular weight of 160,000 Daltons" (claims 6, 22, 38, 52, 65, 74); "an agent attached to said carrier" (claim 17).

Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed.

Furthermore claims 17-20, 22-32, 71, 72, 74-96 are not supported by the description (Art. 5 PCT). No support is to be found throughout the application document as filed disclosing the claimed conjugates wherein the agent is an anti-cancer agent, in particular paclitaxel neither the use of the said conjugates as claimed.

The only effective disclosure showing conjugates (description pages 27-30) describe 125I-aprotinin and aprotinin-biotin conjugates not encompassed under the said denomination of anticancer agent conjugate as claimed.

A mere generic enumeration of anticancer agent and not the particular paclitaxel as part of the therapeutic agent is done regardless of its forming part of a conjugate construct (page 15, paragraph 2) and therefore cannot be considered as sufficient disclosure for the skilled person in order to perform the invention in its whole scope (Ar. 5 PCT).

Support with regard to the first invention is only to be found in the present application for those parts relating to the compounds explicitly disclosed in the examples and those specifically mentioned by chemical name in claims 1, 18, 33, 36, 47, 50, 60, 63, 71.

No international Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item IV
Lack of unity of invention

The Examining Division agrees with the objection put forward by the Search Division as to lack of unity (Rule 13 PCT), the reasons for the objection being as follows:

The problem underlying the present application is the delivery of drugs across the blood-brain barrier for treating disorders of the central nervous system (see page 1, second paragraph).

As solution to this problem several compositions comprising a carrier and an agent attached thereto with different and very diverse chemical and structural characteristics, among which no homology, activity or functional relationship can be inferred, are proposed.

The common feature linking the different inventions together could therefore only be regarded as the use of a carrier (particularly a polypeptide molecule) for the transport of an agent across the blood-brain barrier.

Prior art documents

DE 19953696 discloses Beta-amyloid A4 (homologue of claimed Angio-pep1 according to present application figure 17; description page 32-33) linked to a synzyme. Optionally conjugated to another molecule (see claim 3, fig. 1). The construct is capable for crossing the blood brain barrier (see col. 1 lines 15-32).

Martel C. L. et al in Pharma Sciences (1997), vol. 7, pp. 28-36 disclose the transport of apolipoprotein J bound to soluble amyloid beta 1-40 (homologue to claimed Angio-pep1 according to present application figure 17, description pages 32-33) across the blood brain barrier (see abstract; page 33, col. 2).

Shimura T. et al in Journal of pharmacology and experimental therapeutics (1991), vol. 258, pp. 459-465 discloses that radiolabelled (5-125I-His) ebiratide (adrenocorticotropic hormone analog) is transported through the blood-brain barrier via basic peptide specific

absorptive mediated endocytosis (see abstract, fig 1).

Demeule M. et al in Journal of Neurochemistry (2002) vol. 83, pp. 924-933 describes that P97 (melanotransferrin) could be advantageously employed as delivery system to target drugs, peptides or enzymes directly to the brain (see abstract, discussion).

The common feature mentioned above is consequently not novel and therefore cannot be regarded as linking the inventions together so as to form a single general inventive concept.

As there is no other technical feature which could fulfil the role of special technical feature in the sense of rule 13.2 PCT, the present application lacks unity of invention, containing the following subjects:

1. Claims: 4, 20, 36, 50, 63 complete; 1-3, 6-19, 22-35, 38-49, 52-62, 65-72, 74-96 partially

Carrier for transporting an agent attached thereto across the blood brain barrier wherein the agent is anticancer agent paclitaxel. Conjugate comprising the carrier and paclitaxel, pharmaceutical composition and use of the same for neurological disease (brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke and obesity).

2. Claims: 1-3, 5-19, 21-35, 37-49, 51-62, 64-96 partially

Carrier for transporting an agent attached thereto across the blood brain barrier wherein the agent is a radioactive label. Conjugate comprising the carrier and radioactive label, pharmaceutical composition and use of the same for neurological disease (brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke and obesity)

3. Claims: 1-3, 5-19, 21-35, 37-49, 51-62, 64-96 partially

Carrier for transporting an agent attached thereto across the blood brain barrier wherein

the agent is a green fluorescent protein, a histag protein, and beta galactosidase. Conjugate comprising the carrier and the protein agent, pharmaceutical composition and use of the same for neurological disease (brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke and obesity)

The applicant was informed that the search is the responsibility of the ISA under Chapter I of the PCT, the procedure before the ISA is closed and that there is no provision in the PCT for a review of or an appeal against the findings of the ISA, either by the ISA itself or by the IPEA.

An international search report has only been established for the subject matter of invention 1 as listed above.

No international Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT) (I. e. inventions 2, 3 as listed above)

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claims 85-96 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The applicant's attention is drawn to the fact that the present opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international search report has been drawn up.

No international Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT)

Reference is made to the following documents:

D1: DE 199 53 696 A (CHERKASKY ALEXANDER) 10 May 2001
D2: SHIMURA T ET AL: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 258, no. 2, 1991, pages 459-465.
D3: DEMEULE M ET AL: JOURNAL OF NEUROCHEMISTRY, vol. 83, no. 4, November 2002, pages 924-933.
D4: SEIDEL G ET AL: NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, vol. 284, no. 4, 1974, page R73.
D5: MARTEL ET AL: STP PHARMA SCIENCES, PARIS, FR, vol. 7, no. 1, 1997, pages 28-36.

Novelty Article 33(2) PCT

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3, 6-19, 22-35, 38, 39, 43-46, 59, 71, 72, 74-85, 88 is not new in the sense of Article 33(2) PCT.

D1 discloses Beta-amyloid A4 (homologue of claimed Angio-pep1 according to present application figure 17; description page 32-33 and embraced consequently as functional derivative as claimed) linked to a synzyme. Optionally conjugated to another molecule (see claim 3, fig. 1). The construct is capable for crossing the blood brain barrier (see col. 1 lines 15-32).
Consequently the subject matter of claims 1-3, 6-19, 22-35, 38, 39, 43-46, 59, 71, 72, 74-85, 88 is not new over D1.

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Inventive step Article 33(3) PCT

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96 does not involve an inventive step in the sense of Article 33(3) PCT.

The problem underlying the present application is the delivery of drugs across the blood-brain barrier for treating disorders of the central nervous system (see page 1, second paragraph).

As solution to this problem a composition comprising a carrier wherein aprotinin and Angio-pep1 linked to an anticancer agent, in particular paclitaxel is proposed as the first invention.

Previously discussed document D3, which can be considered the closest prior art, already addresses the problem of delivery of drugs across the blood brain barrier with the use of P97 (melanotransferrin) as delivery system to target drugs, peptides or enzymes directly to the brain (see abstract, discussion).

The difference between D3 and the subject matter of present claims 1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96 is the fact that the particular conjugate of aprotinin or Angio-pep1 with an anticancer agent (as paclitaxel) neither the use for the specific treatment of neurological diseases consisting on brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer, Parkinson, Huntington, stroke, blood brain barrier related malfunction disease, obesity are explicitly disclosed in D3.

Nevertheless, D1 renders obvious the use of a beta-amyloid A4 homologue (as the claimed Angio-pep1) conjugated to another molecule as such construct is capable for crossing the blood brain barrier (see col. 1 lines 15-32; claim 3).

The use of aprotinin is also rendered obvious to the skilled person in view of the teaching of D4, where the effect of **trasylol** (namely aprotinin) in increasing the brain concentration of drug harmine by affecting on the permeability of the blood brain barrier in relation to lymphostatic encephalopathy is described (see abstract).

Furthermore the attention of the applicant is drawn to the fact that all embodiments covered by the claims should satisfy the criteria of inventive step. When the inventive step is solely based on the achievement of a technical effect, such as "transporting of an agent across the blood brain barrier", substantially all embodiments of independent claim 1 should exhibit this effect.

It should be credible that all the alternatives encompassed by the claims are a solution to the problem.

However, it is evident that the number of compounds encompassed under: "agent is releasable form said carrier after transport across the blood brain barrier" (claims 12, 28, 44, 57, 68, 80); "agent is released form said carrier after transport across the blood brain barrier" (claims 13, 29, 45, 58, 69, 81); "a functional derivative" (claims 1, 17, 33, 47, 60, 71); "a drug", "a medicine", "an anticancer agent", "a molecule active at the level of the central nervous system" (claims 3, 19, 35, 49, 62, 71); "agent has a maximum molecular weight of 160,000 Daltons" (claims 6, 22, 38, 52, 65, 74); "an agent attached to said carrier" (claim 17) is such that it is unlikely that all of them posses the effect claimed.

Therefore, as part of the subject matter of claims 1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96 is unlikely to exhibit this particular technical effect in a credible manner, said subject matter cannot involve inventive step.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO03009815	06/02/2003	25/07/2002	25/07/2001

This earlier application shows:
LRP (low density lipoprotein related) receptor ligands including aprotinin and P97 with functional effect on transcytosis (see page 4; fig 17; claim 25) . Conjugates of the same with therapeutic active agents including paclitaxel (see page 37, line 8).
Uses of the same for the treatment of neurological disorders are also described (see claim 8).

Thus, it would be prejudicial to the novelty of the subject-matter of claims 1-4, 6-20, 22-36, 38-50, 52-63, 65-72, 74-96 of the present application.